Metabolism

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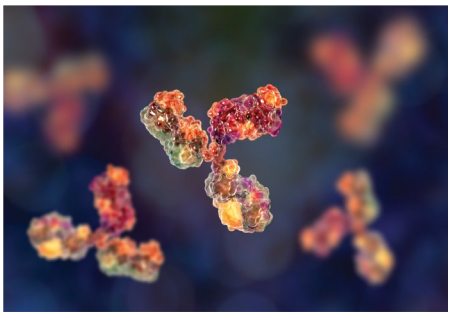
IgG is an early driver of aging

Antibodies are a major effector of the adaptive immune response to infection. Of the antibody classes, immunoglobulin G (IgG) constitutes the most abundant circulating form, and has a long half-life thanks to a recycling mechanism that is reliant on the IgG recycling receptor FcRn. Although IgG-based immune therapies are clinically available for the treatment of age-related diseases (including Alzheimer's disease), whether endogenous IgG has a role in aging has remained unknown. A study by Lexiang Yu et al. has now established that IgG accumulates during aging in mice and humans – particularly in adipose tissue – and that preventing this accumulation can benefit mouse healthspan and lifespan.

"While most people have been interested in identifying longevity factors from heterochronic parabiosis experiments of young and aged mice, we were intrigued by the fact that the young mice aged faster upon exposure to an aged circulation, implying the existence of aging factors", explains Li Qiang, one of the corresponding authors of the study.

"In our previous study, we found that adipose tissue is an aging driver. Here, we focused on adipose tissue to look for aging factors by mass spectrometry. It turned out that the most upregulated proteins were immunoglobulins. We were told that they should be background proteins to discard, but we were interested in their age-related accumulation", continues Liheng Wang, the other corresponding author.

Indeed, the team observed a strong accumulation of IgG in particular (as well as an increase in IgM and IgA) in male and female mice, across several tissues and in plasma: IgG showed a particularly strong and early



accumulation in adipose tissue, from as early as 4 months of age.

Calorie restriction, however, rescued this accumulation of IgG in middle-aged mice. Further, when IgG was administered (via intraperitoneal injection) to young mice on calorie restriction, IgG selectively accumulated in adipose tissues and abolished the beneficial effects of calorie restriction on suppressing markers of senescence and inflammation, and on improving insulin sensitization and adipogenic gene expression, which suggests that there are deleterious functional consequences of age-related IgG accumulation.

Indeed, the authors also demonstrated that IgG treatment was sufficient to induce adipose tissue fibrosis in young mice, and propose a mechanism in which IgG-exposed macrophages induce a fibrotic response through upregulation of TGFβ.

"To next explore whether blocking the accumulation of IgG could be beneficial in aging, we used B-cell-null mice that are deprived of IgG. In these mice, we observed improved metabolic health as well as decreased fibrosis and inflammation during aging; effects prevented by administration of IgG. Then, to more directly manipulate IgG levels without compromising B cell function, we developed a mouse model to specifically prevent IgG accumulation (without affecting IgA or IgM) by knocking out FcRn in macrophages. Age-related IgG accumulation in adipose tissue was strongly reduced in these mice, and healthspan and lifespan were prolonged", explains Wang.

Importantly, the authors showed that IgG also accumulates with age in humans, using western blotting analysis of fat biopsies. Furthermore, they also designed an antisense oligonucleotide that targets FcRn and that successfully decreased IgG levels in aged mice and improved metabolic health, which demonstrates the therapeutic relevance of targeting the IgG recycling mechanism in aging.

Looking forward, Qiang reflects "We are now expanding our investigation of IgG to other aging-related complications beyond metabolic dysfunction. We believe that IgG has broad impacts, particularly in a deleterious manner. Our study also raises the alarm for immune therapies that may boost IgG levels in vivo. There might be potential aging and metabolic detriments."

IgG is a well-established effector of protective immune responses, but this work now identifies a pathogenic role for IgG as an early driver of aging in adipose tissue. Although careful optimization would be necessary to preserve the beneficial effects of IgG, targeting its age-related accumulation provides a new therapeutic strategy in age-related metabolic decline.

Hannah Walters
Nature Aging

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